

PATENT APPLICATION
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Docket No: Q94153

Masao SUDOH, *et al.*

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Examiner: Marcos L SZNAIDMAN

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For: INFUSION PREPARATION CONTAINING (2R)-2-PROPYLOCTANOIC ACID AS
THE ACTIVE INGREDIENT

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Seiichi TANIKAWA, hereby declare and state:

THAT I am a citizen of Japan;

THAT I have received the degree of a Master of Pharmaceutical Sciences in 1995
from Kyoto University;

THAT I have been employed by Ono Pharmaceutical Co., Ltd. since 1995, where I
have engaged in research of infusion preparation;

THAT this declaration is made in support of the above-identified U.S. Patent
Application;

THAT I am a co-inventor of the present application;

THAT the following experiment was conducted by me.

Experiment

[Method]

Disodium monohydrogen phosphate dodecahydrate (8.0 kg) and 5.0 kg of (2R)-2-propyloctanoic acid were added to water for injection. Appropriate amount of sodium

hydroxide was added thereto to adjust the pH to be 8.4 to 9.0, followed by addition of water for injection to be 100 L. After producing uniform solution, it was filtered thorough an aseptic filter (a 0.22 μ m membrane manufactured by Durapore) and the resulting liquid was molded and filled (blow fill-sealed) in a plastic ampoule. The ampoule was sterilized with a high-pressure steam (at 123°C for 15 minutes) to obtain a drug containing (2R)-2-propyloctanoic acid in a concentration of 50 mg/mL. Then 0.2 mL, 2 mL, 10 mL or 20 mL thereof was diluted with a physiological saline to make the total volume 100 mL by which the infusion preparation of the present invention was prepared. Each of sodium ozagrel, citicoline and edaravone which have been known as therapeutic agents for cerebral infarction was dissolved therein in a concentration corresponding to the clinical dose thereof. The changes of compounding as a result of mixing with the infusion preparation of the present invention were investigated. Specifically, changes in the appearance after 24 hours from mixing (with sodium ozagrel or citicoline) or after 48 hours from mixing (with edaravone) were observed by visual and, at the same time, pH of the mixed solution and residual rate of (2R)-2-propyloctanoic acid were measured.

[Results]

As shown in the following table, the infusion preparation of the present invention did not cause changes in the compounding even when it is mixed with the three compounds which have been used for the treatment of cerebral infarction; was colorless and clear even after 24 hours or 48 hours from the mixing; and maintained the pH near neutral region by which administration to living body is possible. Furthermore, the residual rate of (2R)-2-propyloctanoic acid after completion of each of the tests was 95% or more in all cases.

The infusion preparation of the present invention is a infusion preparation which makes a water-insoluble (2R)-2-propyloctanoic acid soluble in water and does not require the operation such as dissolution or dilution at the time of use. Moreover, it exhibits unexpected properties that, even if the pH changes as a result of mixing with other pharmaceutical agent, neither clouding nor precipitation occurs and stability is excellent.

	Concentration of (2R)-2-propyloctanoic acid in saline			
	0.1 mg/mL (10 mg/100 mL)	1 mg/mL (100 mg/100 mL)	5 mg/mL (500 mg/100 mL)	10 mg/mL (1000 mg/100 mL)
Sodium ozagrel (20 mg/100 mL)	clear and colorless (pH:7.5)	clear and colorless (pH:7.8)	clear and colorless (pH:8.0)	not tested
Citicoline (500 mg/100 mL)	clear and colorless (pH:7.2)	clear and colorless (pH:7.8)	not tested	not tested
Edaravone (15 mg/100mL)	not tested	clear and colorless (pH:6.8)	clear and colorless (pH:7.4)	clear and colorless (pH:7.6)

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 2010. 1. 19.


Seiichi TANIKAWA